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CAROTID-CARDIAC BAROREFLEX: RELATION WITH ORTHOSTATIC HYPOTENSION FOLLOWING SIMULATED MICROGRAVITY AND IMPLICATIONS FOR DEVELOPMENT OF COUNTERMEASURES

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Abstract - In a series of studies, we have examined the effects of exposure to simulated microgravity, varying states of vascular volume, and acute exercise on the function of the carotid-cardiac baroreflex in man. In the first study, exposure to simulated microgravity (6° headdown bedrest) reduced the sensitivity and buffer capacity of the vagal baroreceptor-cardiac reflex mechanisms and this impaired baroreflex function was associated with orthostatic hypotension. Since the reduction in plasma volume during BR was not correlated with impaired baroreflex function, a second study was conducted which demonstrated that the carotid-cardiac baroreflex response was not affected by either acute hypovolemia or hypervolemia. These results suggest that acute fluid replacement prior to reentry may not reverse impaired baroreflex function associated with postflight hypotension. In a third study, we demonstrated that one bout of maximal exercise increased baroreflex sensitivity and buffer capacity through 24 h post-exercise. These baroreflex changes were opposite to those observed following BR. Taken together, these data suggest that the contributions of reduced blood volume and impaired carotid-cardiac baroreflex function to orthostatic hypotension following exposure to microgravity are probably separate and additive; maximal exercise in addition to fluid replacement may provide an acute effective countermeasure against postflight hypotension.

INTRODUCTION

Development of orthostatic hypotension following spaceflight has been reported in both U.S. and Soviet space programs. However, mechanisms underlying postflight orthostatic hypotension are unclear, making the development of effective countermeasures difficult, particularly for long duration missions. Reduced blood volume contributes to, but probably is not a sufficient explanation for post-spaceflight orthostatic hypotension [1]. Another possibility is that impaired baroreflex function after reentry impairs hemodynamic adjustments to standing.

In this paper, data obtained from a series of three experiments conducted in the Human Life Sciences Research Laboratory at the Kennedy Space Center will be presented and discussed in an effort to examine the function of the carotid-cardiac baroreflex in man and how it is affected by exposure to simulated microgravity, by varying states of vascular volume, and by acute exercise. The results provide practical implications for present use and future development of countermeasures against postflight orthostatic hypotension.

BAROREFLEX MEASUREMENT

In all three studies, carotid baroreceptor-cardiac reflex responses were measured with a method described previously [21]. Briefly, a stepping-motor driven bellows was used to deliver a series of pressure and suction steps to a Silastic neck chamber. During held expiration, a pressure of 40 mmHg was delivered to the chamber and held for five R-waves; then, with the next R-wave, the pressure sequentially stepped at maximum rates in excess of 300 mmHg/s to approximately 25, 10, -5, -20, -35, -50, and -65 mmHg, and then returned to ambient pressure. Pressure steps were triggered by R-waves so that neck chamber pressure changes were superimposed upon naturally-occurring carotid pulses. This timing was chosen so that experimental baroreceptor stimuli would be as physiologic as possible. With this technique, arterial pressure changes are small [21]. During each test session the stimulus sequence was repeated 7 times and the data averaged for each subject. Baroreceptor stimulus-sinus node response relations measured in this way are highly reproducible. Blood pressures were taken with a sphygmomanometer at the beginning of each test session.

Several measurements were derived for each sequence of carotid baroreceptor-cardiac reflex responses [21]. Carotid distending pressure was considered to be systolic pressure minus neck chamber pressure. Baroreflex stimulus-response relationships were described by plotting R-R intervals for each pressure step against carotid distending pressures. The maximum slope was determined by applying least squares regression analyses to the three consecutive points on the response curve that produced the greatest slope. The R-R interval range was defined as the difference in the maximum and minimum R-R intervals.

MICROGRAVITY EFFECTS

Prolonged 6° head-down bedrest has been used to simulate hemodynamic changes that occur when humans are exposed to microgravity [1,3,6,19]. We used this model in the first study to determine 1) if there are alterations in the carotid baroreceptor stimulus-cardiac reflex response relation following prolonged exposure to simulated microgravity, and 2) if changes in baroreflex function (if they occur) are related to blood pressure responses during post-bedrest standing. Our results have been previously reported [7,8] and indicate that impairment of vagal baroreflex function occurs during head-down bedrest and is associated with dysfunction of hemodynamic adjustments to standing, and support the notion that baroreflex impairment may contribute to orthostatic hypotension following spaceflight.

Eleven healthy nonsmoking normotensive men, with a mean (±SE) age of 38 ± 2 years (range 30-45), a mean height of 179 ± 2 cm (range 173-188), and a mean weight of 79.0 ± 2.0 kg (range 67-93), volunteered to participate as subjects in this study. During a 3-week orientation testing period which preceded the study, all subjects were made familiar with the laboratory, the protocol, and procedures. The experimental protocol comprised 9 d of ambulatory control (C) followed by 30 d of 6° head-down bedrest (BR) and 5 d of post-bedrest recovery (R). During bedrest, the subjects remained head-down without interruption. Each subject underwent a carotid-cardiac baroreflex test on the fourth day prior to bedrest (C4), on days 1, 3, 12 and 25 during bedrest (BR1, BR3, BR12, and BR25), and on days 2 and 5 of recovery (R2 and R5). In addition, the subjects returned to the laboratory after 25 days of uncontrolled recovery (R30) for a final baroreflex test. During the pre-bedrest control and post-bedrest recovery tests, a 30-min supine rest period preceded each session. Resting plasma volume was measured on C4, BR3, BR12, and BR25 with an Evans blue dye technique.

A stand test was conducted immediately upon the termination of the 30-day bedrest (R1). The test began with the subject sitting in bed with his feet hanging over the side of the bed not touching the floor for 60 min. Immediately following the sitting, subjects underwent a 5-min active stand test. The subjects were instructed to stand still with their feet placed 12 inches apart, with their weight evenly distributed, and to refrain from moving. Thus, contractions of the leg muscles were those required to support stationary standing. Blood pressure and heart rate were measured at the end of minutes 3 and 5 of standing.

Average baroreflex response relations for all subjects are depicted in Fig. 1. These relationships demonstrate that both maximum slopes and ranges of responses decreased progressively with continuing bedrest, and did not return to baseline values by the fifth day of recovery. Thus, exposure to simulated microgravity causes significant impairment of carotid-cardiac vagal baroreflex function.

Blood volume reduction has been suggested as one possible mechanism responsible for impairment of baroreflex function [15]. Mean resting plasma volume for all subjects decreased by approximately 15% by BR3, but showed no further reduction through the end of bedrest. There was no significant correlation between changes of plasma volume during bedrest and changes of baroreflex slopes ($r = -0.17$, $P = 0.376$). Thus, the time courses of changes in plasma volume and sensitivity of the baroreflex stimulus-response relationship were

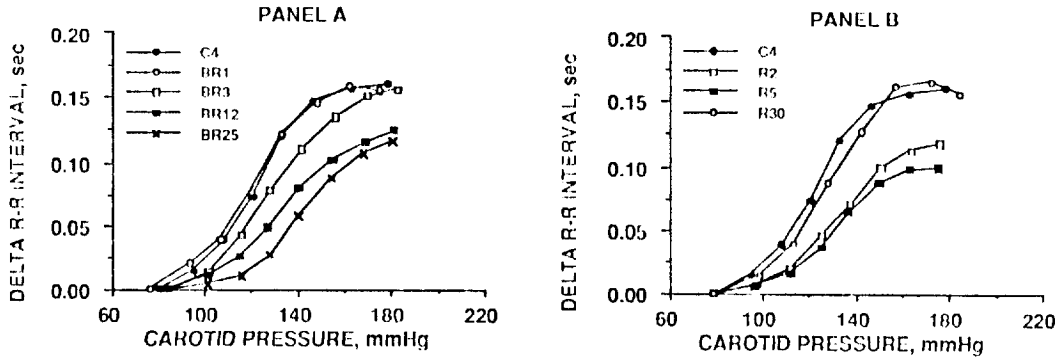

Fig. 1. Carotid baroreceptor cardiac reflex response relationships. Panel A depicts relationships generated on days 1, 3, 12 and 25 of bedrest (BR) and the pre-bedrest control day (C4). Panel B depicts relationships generated on days 2, 5 and 30 of post-bedrest recovery (R) and C4.

not parallel. Plasma volume fell significantly by the third day of bedrest, at a time when maximum slope of the baroreflex response relation had not changed. After the initial 3 days of bedrest, plasma volume remained at constant, low levels for the remainder of bedrest, but maximum baroreflex slopes declined progressively between days 12 and 25. Plasma volume was restored to control levels within the first day of post-bedrest ambulation, but maximum baroreflex slopes remained depressed for at least 5 days after bedrest. Although our data do not rule out a contribution from reduced blood volume, they point away from reductions of blood volume as a primary cause of baroreflex abnormalities that developed during bedrest.

Complete data from the stand test were obtained for ten subjects. Four subjects experienced syncope or presyncope, and the remaining six subjects tolerated the posture test with no noticeable difficulty. Although heart rate increased with standing in both syncopal (+23 ± 5 bpm) and non-syncopal (+49 ± 10 bpm) subjects, the increase was significantly less ($P < 0.05$) in the syncopal group. Non-syncopal subjects maintained the same systolic pressure during pre- and post-bedrest, but syncopal subjects experienced significant reductions of systolic pressures. Thus, compared with subjects who tolerated upright posture well following bedrest, syncopal subjects demonstrated an inability to increase heart rate adequately, despite a greater unloading of baroreceptors (that is, a greater reduction of systolic blood pressure). Other factors such as reduced circulating blood volume [1,5], increased leg vascular compliance [18], and reduced responses of vasoactive hormones [1,5] may have contributed to orthostatic intolerance. However, reductions ($P < 0.05$) of plasma volume from 47.3 ± 2.6 on C4 to 40.1 ± 1.7 ml/kg on BR25 in non-syncopal subjects were not significantly different from those of syncopal subjects (whose average reduction of plasma volume, from 46.4 ± 1.5 to 42.6 ± 1.7 ml/kg, was actually less). Also, there were no significant differences in vasopressin and catecholamine responses between syncopal and non-syncopal subjects in this study [7,8]. Significant elevations in average calf compliance from pre- to post-bedrest, which have been reported for these subjects [6], did not differ between syncopal (4.0 ± 1.3 to 5.3 ± 0.9 vol%/mmHg) and non-syncopal (4.0 ± 0.5 to 5.1 ± 0.7 vol%/mmHg) subjects.

Syncopal subjects demonstrated greater reductions in maximum slope and buffer capacity (range of R-R interval change) of their baroreflex response relationship than non-syncopal subjects (Fig. 2). The reduction in maximum slope of the response relation from 4.0 to 2.2 msec/mmHg for the syncopal subjects was significantly greater ($P = 0.042$) than the reduction from 3.1 to 2.7 msec/mmHg in the non-syncopal group. The degree of impairment of baroreflex function following bedrest correlated directly with the greater reduction in systolic blood pressure and the smaller tachycardia during standing ($r = 0.70$, $P = 0.030$). Our data may be related to those of Cowley et al. [11] who found that conscious dogs with sinoaortic baroreceptor denervation had smaller heart rate increases and greater blood pressure reductions during upright posture than dogs with intact baroreflexes.

The major findings of this study are that 6° head-down bedrest leads to substantial and progressive impairment of vagally-mediated, carotid baroreceptor-cardiac reflex responses, and that the development of baroreflex malfunction is significantly related to the occurrence of hypotension during post-bedrest standing. Our results raise the intriguing possibility that baroreflex impairment contributes to the

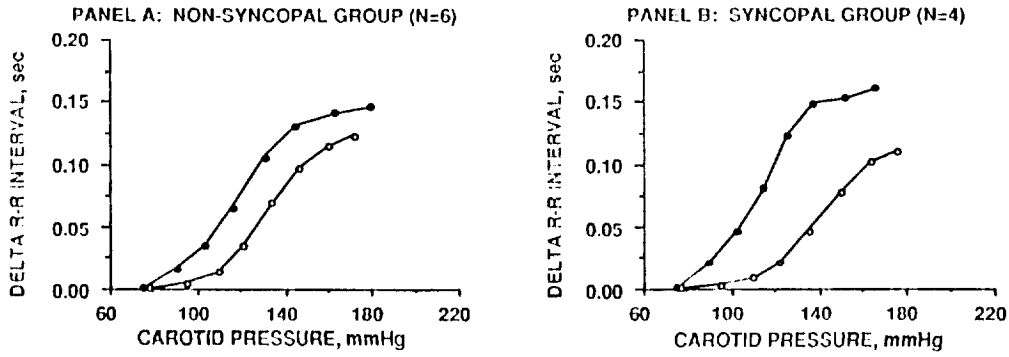

Fig. 2. Carotid baroreceptor-cardiac reflex relationships before (solid circles) and at the end (open circles) of bedrest in non-syncopal (Panel A) and syncopal (Panel B) subjects.

orthostatic hypotension experienced by astronauts after spaceflight. Most United States astronauts experience symptoms of lightheadedness, and some progress to pre-syncope or syncope during standing after spaceflights of 7 to 10 days [1,2]. We hypothesize that as the duration of spaceflight increases, progressive attenuation of baroreceptor-cardiac responses occurs and leads to greater postflight orthostatic intolerance. If this hypothesis is validated, development of effective countermeasures for postflight orthostatic hypotension following projected 90-180 day Space Station missions might have to include techniques to increase vagal-cardiac activity and baroreflex sensitivity prior to reentry.

EFFECTS OF VASCULAR VOLUME

Since reduction in plasma volume has been recognized as a contributing factor to developing orthostatic hypotension, fluid ingestion of isotonic saline is used by U.S. and Soviet crewmembers in an attempt to counteract possible episodes of cardiovascular instability and syncope following reentry. Although partially effective, this countermeasure has not completely restored orthostatic responses to preflight levels following short-term Shuttle flights [2] and following bedrest [17]. One limitation to this countermeasure may be a dissociation between blood volume and the sensitivity of the baroreflex since the time courses of plasma volume loss and impaired baroreflex response observed during bedrest in the first study did not follow in parallel. Therefore, characterization of the effects of blood volume changes on baroreflex responses could provide relevant implications for the development of appropriate countermeasures against orthostatic hypotension following spaceflight. Our second study was therefore designed to determine if stimulus-response relationships of the carotid-cardiac baroreflex would be altered by acute changes in plasma and blood volume that were similar in magnitude and caused similar hemodynamic responses to those reported during actual [10] and simulated [7,8] spaceflight and following fluid ingestion prior to reentry [2].

Eight healthy nonsmoking normotensive men, with a mean (±SE) age of 35 ± 2 yrs , a mean height of 179 ± 2 cm, and a mean weight of 79.5 ± 3.2 kg, volunteered to participate in this study. The experimental protocol required each subject be tested on three separate days, each test day separated by at least one week, in each of three different volemic states; hypovolemia, normovolemia, and hypervolemia. Sequences of test days were randomized to control for possible order effects. Each subject was tested at the same time of day for all tests to control for possible diurinal variations.

Normovolemia was defined as the subject's normal hydration state as it would be on any day of usual and routine activity. Hypovolemia was induced by an intravenous injection of 30 mg of Furosemide. Hypervolemia was accomplished by ingestion of a flavored isotonic solution (0.9% saline) of a volume equal to approximately 2% of lean body mass. The total volume was consumed over 1 h in four equal portions at 15-min intervals.

Immediately after each volemic treatment, subjects underwent 30 min of supine rest (baseline) which was followed by the measurement of the carotid-cardiac baroreflex response relationship. The carotid-cardiac baroreflex test was followed by measurement of plasma volume using Evan's blue dye. Plasma volume measurement was used to verify that we induced changes in vascular volume and maintained them throughout baroreflex testing.

When compared to normovolemia (3510 ± 205 ml), hypovolemia resulted in a reduction in plasma volume equal to 2953 ± 167 ml (15.9%, $P < 0.05$) while hypervolemia increased plasma volume to 3843 ± 218 ml (9.5%, $P < 0.05$). Therefore, a model for reducing vascular volume was verified by a 16% isosmotic plasma volume loss when compared to normovolemia. The magnitude of plasma volume reduction and expansion induced in this study was characteristic of those observed during exposure to actual or simulated microgravity [10] and may provide a model for examining similar effects of hypovolemia and hypervolemia on cardiovascular reflex mechanisms after spaceflight.

Mean carotid-cardiac baroreflex response relationships and parameter estimates across hydration states are presented in Fig. 3. The graph of the response relationships indicates parallel functions across hydration states with no shift in location along the R-R interval axis or the carotid pressure axis. Thus, neither an expanded nor depleted plasma volume altered the response of the carotid-cardiac baroreflex. Threshold and saturation of the reflex, as indicated by carotid distending pressures at minimum and maximum R-R intervals, respectively, were not different between volemic states. Range of the R-R interval response, an index of total buffering capacity of the reflex, and maximum slope, an index of baroreflex sensitivity, were not altered by acute hypovolemia or hypervolemia.

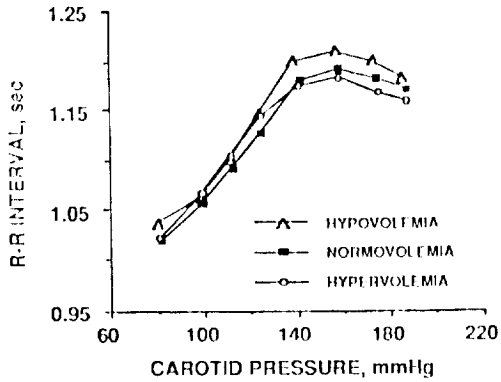

Fig. 3. Stimulus-response relationship of the carotid-cardiac baroreflex during hypovolemia, normovolemia, and hypervolemia.

The degree to which we depleted plasma volume is similar to the hypovolemia induced during spaceflight [10]; thus, the comparison of baroreflex responses between hypovolemic and normovolemic states in our subjects may be analogous to fluid loss during spaceflight and assumed replacement [2] by drinking prior to reentry. In this study, the subjects increased vascular volume above normovolemia rather than restoring it from hypovolemia as astronauts do. However, within a greater range than the normal operational interests of NASA, we have demonstrated that there appears to be no effect of acute volume reduction or expansion on high-pressure baroreceptor responses. These data confirm our earlier observations from the bedrest study that impairment of the carotid-cardiac baroreflex in man following exposure to simulated microgravity appears to occur independent of the accompanying hypovolemia [7,8].

The ability of astronauts to conduct safe and effective performance of tasks required during exposure to G forces of reentry, potential emergency egress immediately following landing, or return to postflight job activities, is of considerable concern to NASA. Salt and water loading prior to reentry has been used as an acute countermeasure and demonstrated to be only partially effective in reversing the cardiovascular effects of Shuttle missions 2-8 days long [2]. Since our data from the present study demonstrated that normovolemia or expansion of vascular volume by fluid ingestion did not alter the carotid-cardiac baroreflex response compared to hypovolemia similar in magnitude of that induced by spaceflight, it may be that currently employed fluid loading procedures will be less effective as spaceflight missions exceed two to three weeks duration.

The major finding of this study was that acute changes in vascular volumes did not affect the response of the carotid-cardiac baroreflex. We interpret these results as indicating that if impaired high-pressure baroreflexes contribute to the development of postflight orthostatic hypotension [7,8], then some countermeasure other than fluid replacement may be required to provide cardiovascular stability following prolonged exposure to microgravity.

MAXIMAL EXERCISE EFFECTS

Extensive exercise has been used in both U.S. and Soviet space programs in an effort to reverse or minimize several physiologic adaptations which may compromise the health, safety and productivity of astronauts, including postflight orthostatic instability. If exercise were to be effective in countering postflight orthostatic hypotension, it seems reasonable that an exercise profile would have to be specifically designed to reverse vagal baroreflex impairment. We considered the possibility that an acute, intense bout of exercise rather than conventional longterm training might enhance baroreflex response since one episode of maximal exercise has provided protection against orthostatic instability and episodes of fainting following short-term exposure to simulated microgravity [22]. Therefore, in the third study, we performed repeated measurements of the carotid baroreceptor stimulus-cardiac reflex response relationship during the 24 h following exposure to an acute maximal exercise. Our results supported our hypothesis that a single bout of maximal dynamic exercise may represent an effective countermeasure for postspaceflight orthostatic instability by acutely increasing the responsiveness of the vagal baroreflex.

Eight healthy normotensive men, with a mean (±SE) age of 32 ± 6 yrs, a mean height of 180 ± 6 cm, a mean weight of 78.2 ± 9.0 kg, and a mean maximal oxygen uptake (VO_2max) measured on the cycle ergometer of 46.2 ± 6.5 ml/kg/min, served as subjects. On a random basis, each subject completed two experimental protocols that entailed periodic tests of the carotid-cardiac baroreflex 1) before and after a maximal supine exercise bout, and 2) during a control (no maximal exercise) session. Each protocol spanned 24 h, with a minimum of one week intervening between the two sessions. Subjects performed a multistage supine exercise test on a Quinton (model 845B) electronically-braked cycle ergometer which consisted of continuous graded work intensities at a pedaling frequency ranging from 60-70 rpm. The workrate for the initial 4 min was 200 kpm/min, after which the workrate was increased each minute by 100 kpm/min increments until the subject reached volitional exhaustion. In this way, the duration of the exercise lasted no longer than 15-20 min. Subsequently, carotid baroreflex tests were made at 3, 6, 12, 18, and 24 h postexercise, with at least 30 min in the supine position preceding each. Exactly the same protocol at the same 24-h clock times was followed on the other experimental day with the exception of the maximal supine exercise bout.

All blood pressure and baroreflex response parameters were unaltered throughout 24 h in the control treatment. The average stimulus-response relationships of the baroreflex for all 8 subjects at preexercise (0 h) and 12 h postexercise are depicted in Fig. 4. Figure 5 demonstrates that exercise significantly increased both maximum slopes and ranges of responses by 3 h postexercise and remained above preexercise values by 24 h of recovery compared to the control treatment. These plotted relationships demonstrate exercise induced a change in the shape of the curve, i.e., increased slope and range of minimum to maximum R-R interval. Therefore, the major finding of this study was that high intensity exercise leads to substantial and prolonged increase in the sensitivity and total buffer capacity of the baroreflex through at least 24 h of recovery.

Ineffectiveness of using extensive aerobic exercise of moderate intensity and long duration to counteract orthostatic instability following exposure to actual and simulated microgravity may represent the failure to identify and employ a specific exercise profile that reverses or attenuates the baroreflex impairment associated with orthostatic hypotension reported in our first study. Exercise prescriptions used during long duration spaceflight have primarily consisted of conventional daily repeated dynamic exercise on a cycle or treadmill ergometer for durations of 30 min to 2.5 h per day [10]. Groundbase experiments in which bedrest was used as a microgravity analog have included the use of similar exercise training protocols. Unfortunately, conventional dynamic and resistive training in 1G employing daily submaximal work outputs have failed to produce any chronic changes in the sensitivity of the carotid-cardiac baroreflex [9,20,23]. Thus, in light of the relationship between impaired baroreflex response and orthostatic hypotension following exposure to simulated microgravity, it is not surprising that exercise training that fails to alter baroreflex sensitivity in 1G cannot provide protection against orthostatic instability

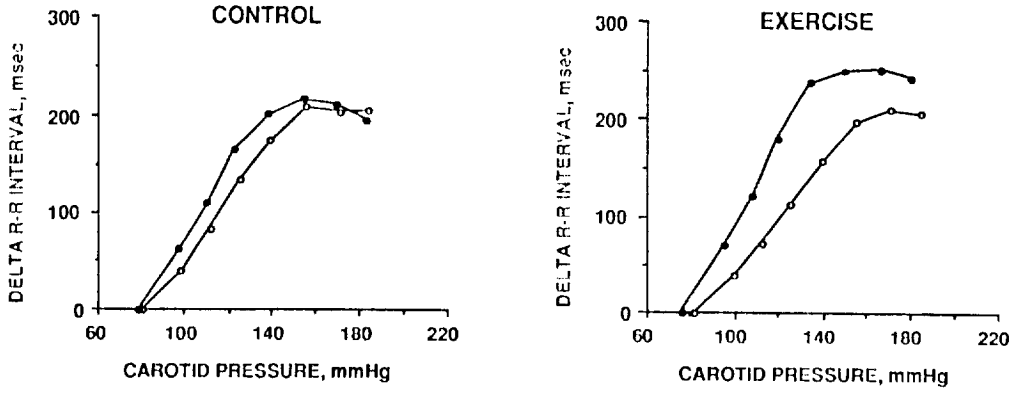

Fig. 4. Average carotid baroreceptor-cardiac reflex response relationships for all subjects (N = 8) at preexercise (open circles) and at 12 h postexercise (closed circles) during control (left panel) and exercise (right panel) treatments.

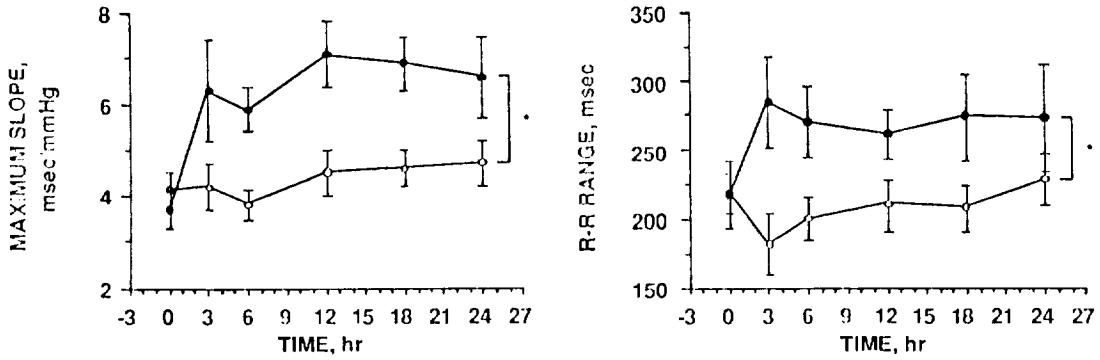

Fig. 5. Maximum slope (left panel) and R-R interval range (right panel) during 24-h period with (closed circles) and without (open circles) maximal exercise. Symbols represent the mean (circles) and ±1 SE (lines) for all subjects (N = 8). Time 0 represents baseline resting values. Asterisk indicates significant treatment effect ($P < 0.05$).

following actual or simulated spaceflight.

Our observation that maximal dynamic cycle exercise acutely increased the sensitivity of a cardiovascular reflex is not without precedent. There is evidence to suggest that the use of graded maximal exercise can acutely restore various cardiovascular and metabolic capacities attenuated by exposures to simulated microgravity or physical deconditioning. Exposure to simulated microgravity or physical deconditioning has reduced insulin receptor sensitivity in man [13,16]; one bout of maximal exercise following 10 days of detraining returned insulin sensitivity to normal levels [16]. One bout of maximal exercise at the end of 10 days of bedrest restored VO_2max, heart rate, blood pressures, rate-pressure-product, oxygen pulse, endurance time and orthostatic stability on a treadmill to pre-bedrest levels within two hours of ambulation [4]. Two primary mechanisms associated with the development of postflight orthostatic hypotension appear to be reduced blood volume [2] and impaired baroreflex activity [7,8]. Acute expansion of plasma volume has been induced by maximal exercise [14] and reversed the reduction of aerobic capacity and stroke volume during exercise following detraining [12]. In addition, a single bout of maximal exercise has reversed fainting episodes following acute exposure to simulated microgravity [22], an effect which might be related to the increased response of arterial baroreflexes observed in the present study. Thus, our observation that acute maximal exercise increased baroreceptor-cardiac reflex response may represent a more universal response in which the capacity of physiological systems may be increased as part of the general adaptation syndrome manifested during the acute recovery phase of intense exercise.

The reasons for maximal exercise being more effective than extended submaximal levels in restoring VO_2max, plasma volume, cardiovascular capacity, baroreflex function, and orthostatic stability after exposure to simulated microgravity are not clear. However, the use of less frequent and more intense exercise as a possible countermeasure against the loss of cardiovascular and metabolic capacities and development of postflight orthostatic hypotension should be thoroughly explored. Such an exercise prescription is attractive because it would be cost effective by enhancing the maintenance of crew health and postflight recovery while minimizing inflight use of work time, food, water and oxygen for exercise activities. This issue is an important consideration since resources for life support systems are limited.

SUMMARY

Exposure to microgravity impairs the carotid-cardiac vagal baroreflex function and provokes orthostatic hypotension. It was reasonable to hypothesize that an effective countermeasure for postflight orthostatic hypotension should include the ability to reverse shifts of the baroreflex relationship. Changes in vascular volume due to fluid "loading" has little effect; however, acute maximal exercise induces baroreflex change opposite to that of microgravity. This effect is summarized in Fig. 6. We previously hypothesized that the development of effective countermeasures for postflight orthostatic hypotension following long-duration space missions might have to include techniques to increase vagal-cardiac activity and baroreflex sensitivity prior to reentry [8]. Our results from the present study suggest that one bout of dynamic exercise such as graded maximal cycle ergometry may represent such a method. One limitation to

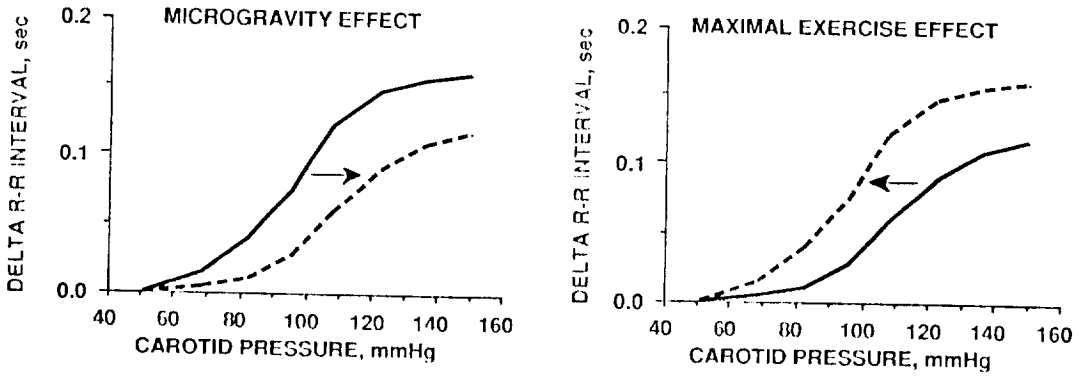

Fig. 6. Diagramatic illustration of the opposite effect of a single bout of maximal cycle exercise compared to exposure to actual or simulated microgravity on the carotid baroreceptor-cardiac response relation. In each plot, the arrow indicates shifting of the relation from before (solid line) to after (broken line).

extrapolating our results to spaceflight conditions is that our exercise experiments were conducted using ambulatory subjects rather than subjects who had baroreflex impairment induced by exposure to simulated microgravity. Although our results do not prove that baroreflex abnormalities caused by exposure to microgravity can be reversed by acute maximal exercise, it seems reasonable to hypothesize that if the baroreflex response can be enhanced in subjects with normal function, then maximal exercise could increase sensitivity in subjects with impaired function. The use of one bout of maximal exercise within 24 h of reentry may represent a tenable countermeasure against the development of postflight orthostatic hypotension. The results from these studies provide a physiological basis for groundbase and spaceflight testing of acute maximal exercise as a protective measure against postflight orthostatic instability.

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